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DEVELOPMENT AND APPLICATIONS OF AN OXAZOLE-FORMING REACTION

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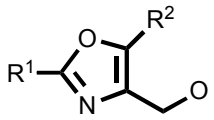
Abstract – We review an oxazole-forming reaction devised in our laboratory. The technique allows the facile assembly of 2,5-disubstituted-4-carbalkoxy oxazoles, including 5-amino and 5-alkenyl oxazoles. Applications of this chemistry in the total synthesis of muscoride A, siphonazoles, and other oxazole alkaloids are described.

INTRODUCTION

Heterocyclic chemistry provides considerable opportunity for the development of new synthetic methods. Indeed, the bioactivity of many heterocycles and the noteworthy architecture of numerous heterocyclic natural products often translate into interesting challenges in the chemical domain. This is certainly the case for a group of natural products that incorporate consecutive 2,4,5-trisubstituted oxazole subunits of the type **1** (Scheme 1). Representative examples of such nitrogenous substances include muscoride A, **2**,[1] diazonamides, **3**-**4**,[2] and telomestatin, **5** (Scheme 2).[3] It should be noted that while segments **1** are fairly rare among natural products,[4] they occur frequently in medicinal agents. For instance, since the beginning of 2010, no fewer than 8 disclosures have described the therapeutic effects of chemical entities incorporating such moieties.[5]



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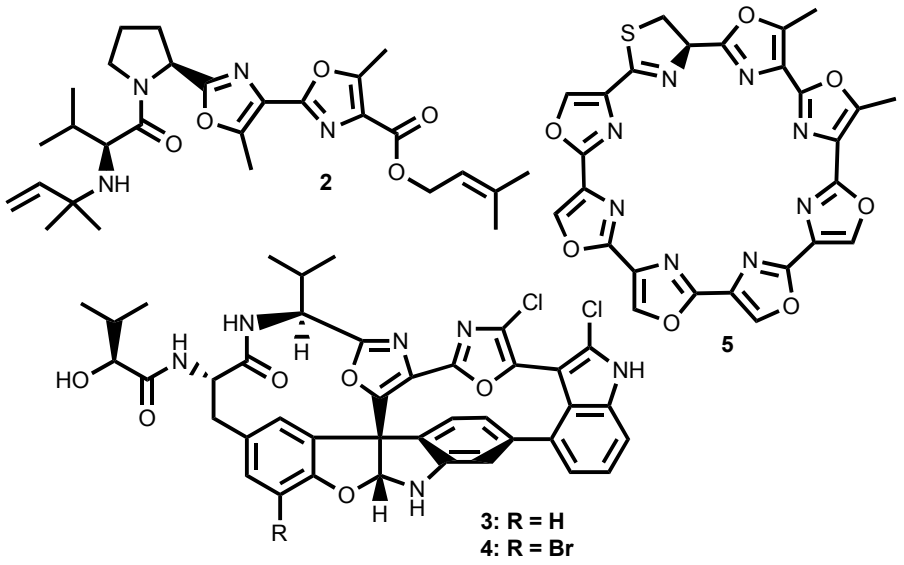
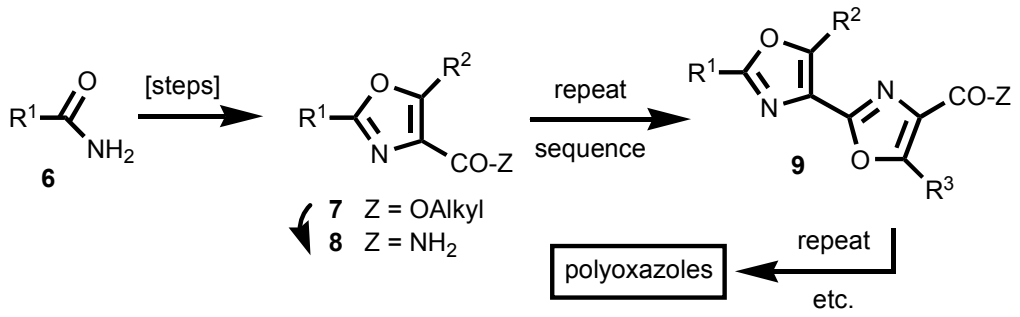
Scheme 1

Dedicated to Professor Albert Eschenmoser on the occasion of his 85th birthday



Scheme 2

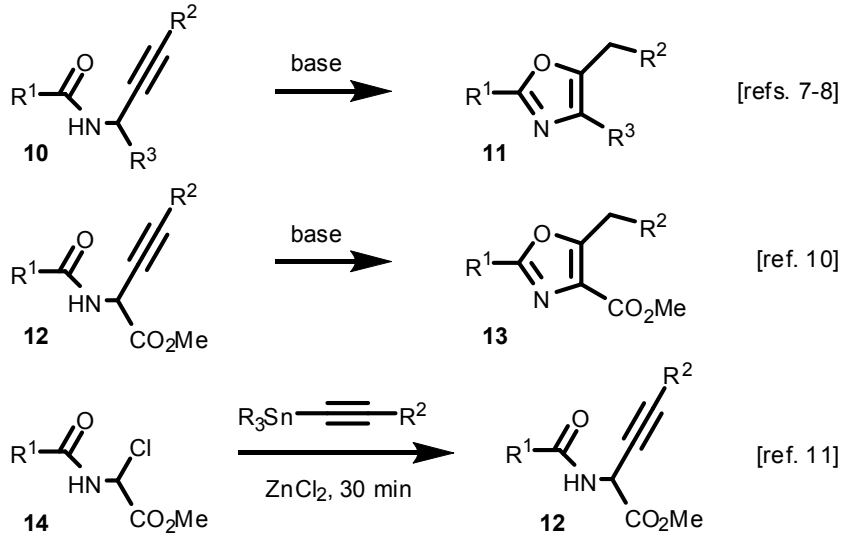
We became interested in natural and non-natural substances that exhibit multiple consecutive copies of subunit **1**. This induced us to ideate an iterative oxazole-forming reaction that would function as seen in Scheme 3. Thus, an appropriate sequence would elaborate a generic primary carboxamide **6** to an oxazole, **7**, which displays a C-4 carbalkoxy group. Conversion of the latter into a primary amido substituent would enable a second cycle of the sequence, leading to a bis-oxazole **9**, also exhibiting a C-4 $CONH_2$ substituent. Multiple iterations of the cycle would produce a polyoxazole construct. Such a methodology was anticipated to be useful both in synthetic organic and in medicinal chemistry. In this paper, we review salient aspects of this chemistry and we discuss selected applications in natural product synthesis and in drug research.



Scheme 3

DEVELOPMENT OF AN ITERATIVE OXAZOLE-FORMING REACTION

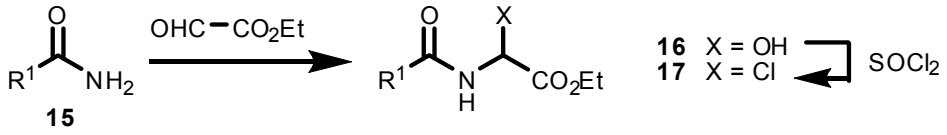
A number of literature precedents influenced the manner in which the surmise pictured in Scheme 3 was



Scheme 4

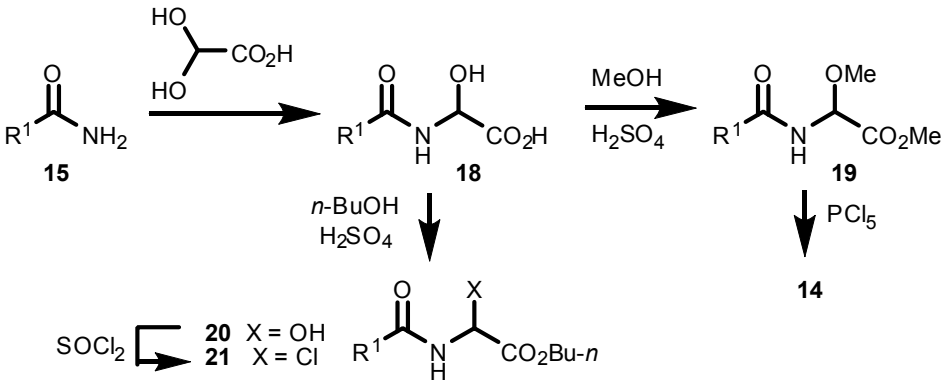
translated into practice. Deryckere,[6] Hacksell,[7] and Wipf,[8] had shown that *N*-propargylic amides **10** (R^3 = H or occasionally alkyl) undergo cycloisomerization to oxazoles **11** (Scheme 4) under Lewis acidic[6] or, more commonly, basic[7,8] conditions.[9] However, **11** lack a requisite 4-COOR substituent. Oxazoles incorporating such a group emerge upon cyclization of alkynylglycinates **12**, as demonstrated by Nagao.[10] Nonetheless, the Nagao synthesis of **12** is fairly laborious. A straightforward route to **12** was described later by Williams (cf. **14** → **12**).[11] We not only reproduced these reactions effortlessly, but we also found that by extending the contact time to ca. 4h one could induce *in situ* cycloisomerization of the transient **12** to oxazoles **13**, which thus become the virtually exclusive products of the reaction (50-55% yield).[12] Unfortunately, the reliance of this chemistry upon alkynylstannane building blocks overshadowed its usefulness. The risk of organotin contamination of downstream products precluded the use of such organometallics for medicinal chemistry research. What we required was a way to achieve a Williams alkynylglycinate construction with acetylenic nucleophiles incorporating a nontoxic metal, with the presumption that a subsequent cycloisomerization of the resultant **12** would produce the desired oxazoles.

A few words about chloroglycinates **17** are in order at this point. These substances are readily available by the method of Ben-Ishai,[13] which entails the initial combination of a primary amide (or carbamate) with ethyl glyoxylate, followed by $SOCl_2$ treatment of the adduct **16** (Scheme 5). They are reactive, water-sensitive, and are difficult to purify. Fortunately, they emerge in a state of satisfactory purity and are best used in crude form. They are also storable for several months at –20 °C if adequately protected from moisture. Scheme 5 depicts our preferred method to prepare such chloroglycinates, but other routes are known. For instance, Williams obtained **14** by reaction of **19** with PCl_5. In turn, **19** results when the



Scheme 5

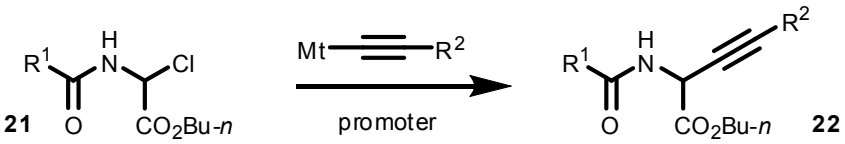
adduct of a primary amide (or carbamate) with glyoxylic acid hydrate is treated with MeOH and catalytic H_2SO_4. This induces simultaneous methyl ether formation/Fischer esterification. It is worthy of note only Fischer esterification occurs when MeOH is replaced with a higher alcohol, e.g., *n*-butanol (cf. 94% yield of **20**, R^1 = Ph).[12] Compounds **20** thus become accessible even if the corresponding glyoxylic ester is unavailable, and subsquent $SOCl_2$ treatment advances them to the expected chloroglycinates (Scheme 6).

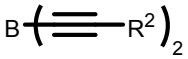


Scheme 6

The ready availability of chloroglycinate educts induced us to study their Metcalf-type condensation[14] with the trimethylsilyl derivative of terminal alkynes under the influence of $AlCl_3$. While analogous chloro substrates combine efficiently with bis-TMS acetylene under these conditions, other 1-TMS-1-alkynes failed to react (Table 1). Equally disappointing results were obtained when we attempted to induce a Petasis-like condensation[15] of **21b**, **21e**, or **21f** with alkynylboronic esters, with or without Lewis acid promoters. A glimmer of hope initially provided by the reaction of **21g** with trialkynylboranes, prepared in situ from lithium acetylides and BBr_3, soon vanished when we found ourselves unable to obtain the desired **22g** in greater than 20% yield. Exposure of **21** to alkali metal acetylides (Li, Na, K) triggered rapid degradation to intractable polymeric materials. Some **22** emerged in a disastrous 5% yield from the reaction of **21** with a Li acetylide in the presence of $ZnCl_2$ or BF_3OEt_2.

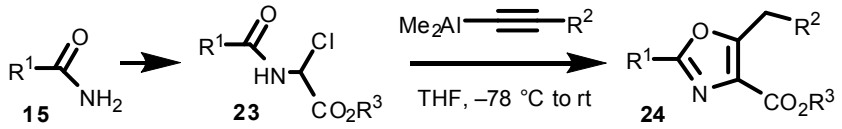
Table 1. Conversion of chloroglycinates into alkynylglycinates with alkynylmetallic agents

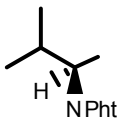
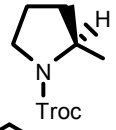
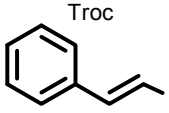
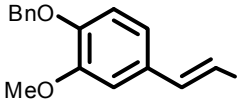


entry	R^2	X	Mt	promoter	% yield
a	*n*-C_6H_{13}	Cl	$SiMe_3$	$AlCl_3$	–
b	*n*-C_6H_{13}	Cl	B(O-*i*Pr)$_2$	none	15
c	*n*-C_6H_{13}	Cl	B(O-*i*Pr)$_2$	$ZnCl_2$	–
d	Ph	Cl	B(O-*i*Pr)$_2$	none	–
e	Ph	OMe	B(O-*i*Pr)$_2$	none	–
f	Ph	OH	B(O-*i*Pr)$_2$	none	–
g	*n*-C_6H_{13}	Cl		$ZnCl_2$	20
h	*n*-C_6H_{13}	Cl	Li	none	–
i	*n*-C_6H_{13}	Cl	Li	$ZnCl_2$	5
j	*n*-C_6H_{13}	Cl	Li	BF_3OEt_2	5
k	*n*-C_6H_{13}	Cl	$AlMe_2$	none	80

Such a lugubrious ingemination of negative results was finally interrupted when, inspired by the work of Negishi[16] and Katritzky,[17] we evaluated alkynylaluminum nucleophiles. We were delighted to find that a reagent produced upon the interaction of lithiated 1-octyne and Me_2AlCl in THF, at –78 °C — arguably, a dimethylaluminum acetylide — rapidly converted the foregoing chloroglycinates into alkynylglycinates in high yield (cf. entry **k**). Moreover, cycloisomerization of the latter to the corresponding oxazoles occurred *in situ* if the temperature was allowed to increase to 25 °C before workup (ca. 2-4 hrs), or if the reaction was worked up under gently basic conditions (aq. $NaHCO_3$). An oxazole-forming reaction

Table 2. Representative oxazoles obtained by the new technique



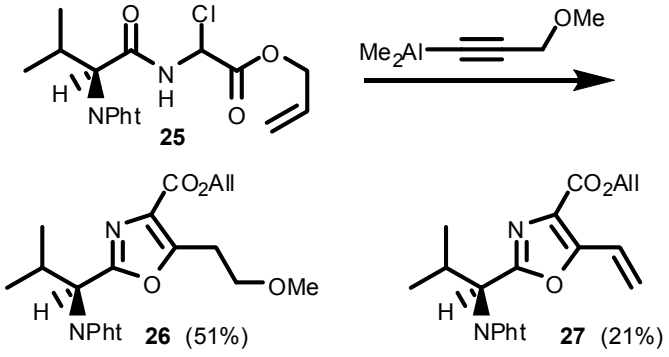
entry	R^1	R^2	R^3	% yield
a	Ph	*n*-C_6H_{13}	*n*-Bu	91
b	Ph	Ph	*n*-Bu	90
c	Ph	$SiMe_3$	*n*-Bu	78
d	Me	*n*-C_6H_{13}	*n*-Bu	68
e	Me	Ph	*n*-Bu	77
f	*c*-C_6H_{11}	Ph	*n*-Bu	84
g	*c*-C_6H_{11}	$SiMe_3$	*n*-Bu	84
h	Ph	$SiMe_3$	Et	46
i	Me	$SiMe_3$	Et	45
j		CH_2OMe	Et	42
k		$SiMe_3$	Et	72
l		$SiMe_3$	Et	37
m		$SiMe_3$	Et	15
n	$PhSCH_2$	$SiMe_3$	Et	61

proceeding through the union of a primary amide, a glyoxylic ester, and a terminal acetylene, had thus materialized.[18] Table 2 provides a summary of representative oxazoles obtained by this technique. It

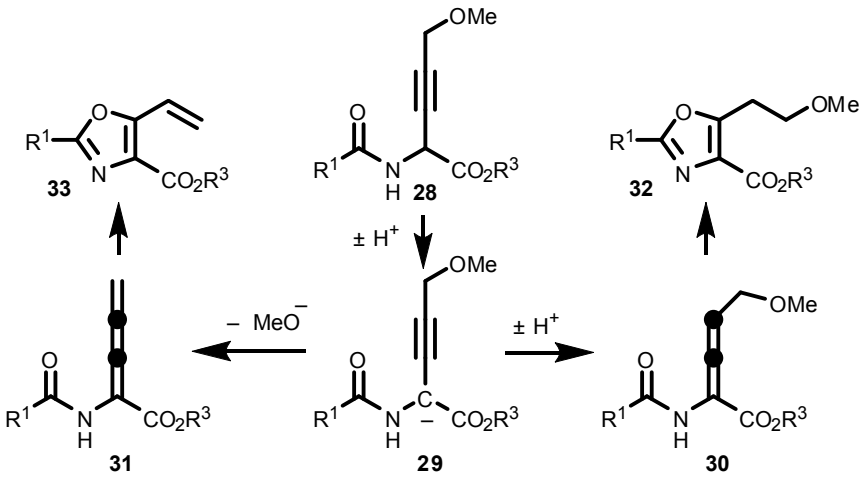
should be noted that the listed yields refer to final products purified by column chromatography. Because chloroglycinates **23** were employed in crude form, such yields reflect substantially the overall efficiency of the conversion of primary amides **15** into the corresponding oxazoles.

The following key points define the scope and the known limitations of the process. Most primary amides — whether aromatic, aliphatic, or aminoacid-derived — may be utilized in the reaction. Higher esters of the glyoxylic portion (cf. *n*-Bu vs. Et) tend to afford better yields. Aminoacid-derived substrates participate in the reaction with no erosion of sterochemical integrity, as determined by the scrutiny of ^{1}H and ^{13}C NMR spectra of the (*R*)-α-methylbenzylamide of oxazoles **24j-k**.[19] A phthalimide protecting group (cf. **24j**) is well tolerated. However, chloroglycinates derived from α,β-unsaturated amides are poor substrates, affording oxazoles in substantially diminished yields. Thioether functionalities are tolerated (cf. **24n**). Conversely, no oxazole was detected among the products originating from chloroglycinate substrates in which group R^1 was equal to $ClCH_2$ or $(MeO)_2P(O)CH_2$.

The dimethylaluminum derivative of methyl propargy ether reacted with **25** to provide a mixture of the expected 5-(2-methoxylethyl) oxazole plus the corresponding 5-vinyloxazole. For example, the reaction of **25** with (3-methoxyprop-1-ynyl)dimethylaluminum returned **26** (51% yield) and **27** (21% yield; Scheme 7). Similar behavior was observed in the reaction of entry **j** of Table 2. The formation of **27** is clearly attributable to a formal loss of methanol from the product; however, experiment revealed that such an eliminative process is unlikely to evolve from **26**. Indeed, exposure of 5-(2-methoxylethyl) oxazole of the type **26** to the action of strong bases (LDA, KHMDS) failed to produce any vinyl counterpart.[20] Evidently, loss of MeOH occurs prior to oxazole formation. The work of Wipf[8] suggests the mechanistic picture outlined in Scheme 8 for the origin of **27** and for the overall conversion of alkynylglycinates into oxazoles. The initial product of halogen substitution, **28**, is reversibly deprotonated under the basic conditions of the reaction. Protonation of transient anion **29** at the distal position affords cumulene **30** (never detected in our reaction). Disrotatory electrocyclization of such a 6-electron systems and prototropic tautomerism afford **32**. We believe this to be the mechanism by which all alkynylglycinates



Scheme 7



Scheme 8

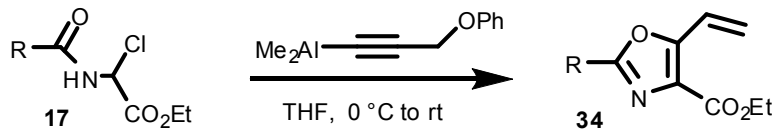
isomerize to oxazoles. On the other hand, the departure of the propargylic nucleofuge (MeO in the case of **29**) results in formation of cumulene **31** (also not detected), which then advances to vinyloxazole **33** by an analogous electrocyclization/tautomerization sequence.

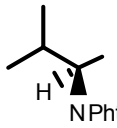
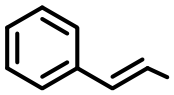
Curiously, the 5-alkenyl-2-alkyl-4-carbalkoxy oxazole motif embodied in **33** has been scantily documented. Generic 5-alkenyloxazoles have been prepared by cycloisomerization of appropriate *N*-propargylamides,[8] Pd-mediated coupling reactions,[21] dehydration of alcohols obtained by reduction of 5-acyloxazoles,[22] "long range Pummerer cyclization" of certain sulfur-substituted propargylamides,[23] olefin metathesis of preformed 5-alkenyloxazoles,[24] and Wittig reaction of 5-formyloxazoles.[25] The 5-vinyloxazole system is particularly rare, a mere 17 examples of it having been recorded in the CAS database as of this writing.[26] On the other hand, 5-alkenyloxazoles in general, and especially compounds **33**, are clearly valuable building blocks in heterocyclic chemistry. In addition, they appear as subunits of particular β-lactam antibiotics[27] and antiviral agents.[28] This induced us to establish improved routes to the 5-alkenyl series based on the new oxazole-forming process.

When the chemistry of Scheme 7 was implemented by using a dimethylalkynyl aluminum reagent derived from phenyl propargyl ether, the result was the virtually exclusive formation of 5-vinyl oxazoles, albeit in moderate yield.[29] Representative examples are listed in Table 3, which underscores the fact that chloroglycinates derived from α,β-unstaurated amides react poorly in this transformation (entry **g**). Evidently, the greater nucleofugal character of $PhO^{(-)}$ relative to $MeO^{(-)}$ favored the eliminative pathway leading from **29** to **31**, and thence to **33**.[30] We note also that presumed aluminum reagents produced from lithiated propargyl chloride afforded mixtures of products containing no oxazole.

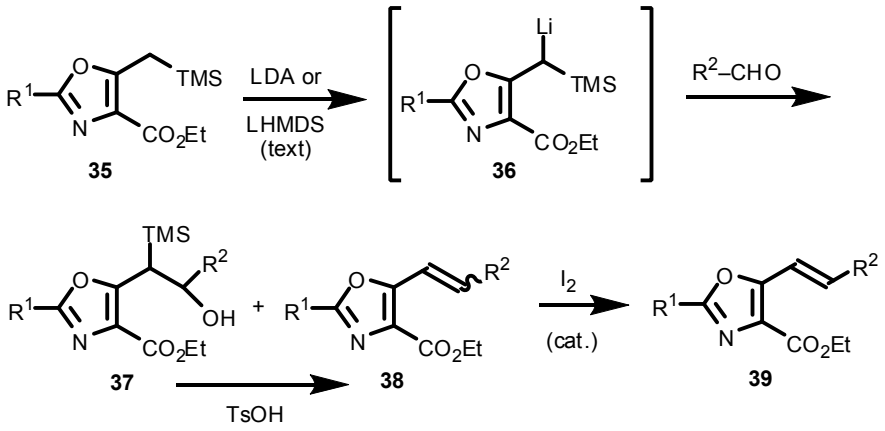
The facile access to 5-trimethylsilylmethyl oxazoles provided by the chemistry of Table 2 (entries **c** and **g**-**n**) permitted the development of a Peterson avenue to more complex 5-alkenyl oxazoles as delineated

Table 3. Representative 5-vinyloxazoles obtained by the new technique



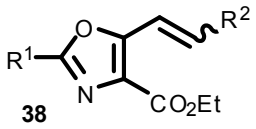
entry	R	% yield
a	Me	41
b	*c*-C_6H_{11}	50
c	Ph	36
d	Bn	39
e	$PhSCH_2$	41
f		55
g		< 10

in Scheme 9.[31] Deprotonation of oxazoles **35** afforded a benzylogous silicon-stabilized enolate, **36**, which was relatively unreactive, even toward aldehydes. Accordingly, the addition of **36** to aldehydes was carried out in the presence of $TiCl_4$. Experiment revealed that substrates in which R^1 is an aromatic group



Scheme 9

Table 4. Representative 5-alkenyoxazoles obtained by Peterson reaction



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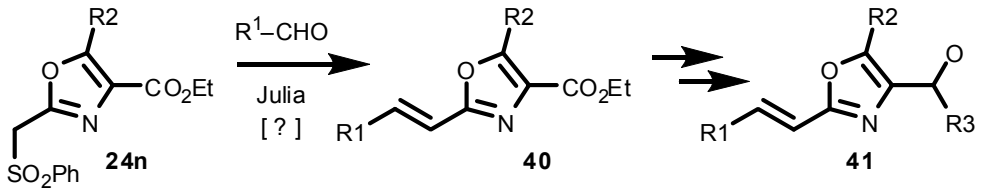
entry	R^1	base	R^2	% yield (*E* : *Z*) [a]	*E* : *Z* [b]
a	Ph	LDA	Et	79 (9 : 1)	
b	Ph	LDA	Ph-$(CH_2)_2$	71 (7 : 3)	
c	Ph	LDA	4-MeO-C_6H_4	74 (7 : 3)	
d	Ph	LDA	2-Me-C_6H_4	53 (1 : 1)	*E* only
e	Ph	LDA	4-Cl-C_6H_4	74 (6 : 1)	
f	Ph	LDA	4-NC-C_6H_4	57 (4 : 1)	
g	Ph	LDA	3-Me-C_6H_4	78 (9 : 1)	
h	Ph	LDA	2-Furyl	50 (4 : 1)	
i	Ph	LHMDS	Ph	83 (3 : 1)	96 : 4
j	Me	LHMDS	Ph-$(CH_2)_2$	56 (3 : 2)	96 : 4
k	Me	LHMDS	4-Cl-C_6H_4	46 (*E* only)	
l	Me	LHMDS	2-Thienyl	77 (*E* only)	

[a]Yield and *E*/*Z* isomer ratio of chromatographically purified products obtained after TsOH treatment (text). [b] *E*/*Z* isomer ratio after I_2 treatment (quant. yield).

reacted best when lithiation was effected with LDA, while LHMDS was often the base of choice if R^1 was a small alkyl such as a methyl group. On the other hand, while the strongly Lewis acidic $TiCl_4$ favored carbonyl addition, it retarded the (formal) elimination of TMS-OH from the adducts,[32] and promoted the formation of mixtures of **37** and **38**. Complete conversion of **37** into **38** was achieved by

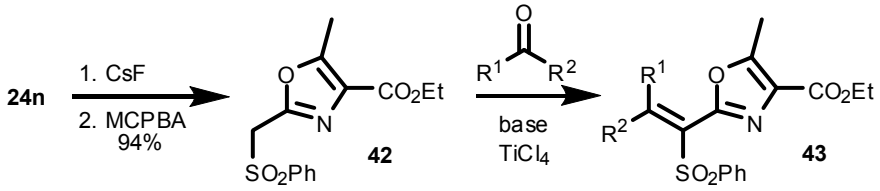
treatment of the crude mixture with TsOH.[33] The ultimate products **38** were obtained as mixtures of *E* and *Z* geometric isomers, the ratio of which appeared to depend on the nature of the aldehyde. Fortunately, nearly complete (> 95:5) isomerization to the *E*-alkene was observed upon refluxing the mixture of olefin isomers in toluene containing a catalytic amount of I_2.[34] Representative examples are listed in Table 4.

The facile formation of oxazole **24n** provided us with an opportunity to revisit a long-standing problem: the Julia olefination[35] of carbonyl compounds with the corresponding sulfone (Scheme 10). This seemingly trivial transformation has eluded the chemical community for decades, and this for a number of reasons.[36] In particular, the anion of 2-sulfonylmethyloxazole-4-carboxylates (cf. **24n**) is an infamously poor nucleophile, failing to add even to aldehydes.[37] A solution to this problem was anticipated to have favorable ramifications in drug research. Indeed, 2-styryloxazoles of the type **41**, R^1 = aryl, appear as subunits of a number of bioactive molecules, including kinase inhibitors,[38] anti-HIV agents,[39] PPAR agonists,[40] MCP-1 receptor antagonists,[41] antiobesity/antidiabetic agents,[42] and anthelmintic substances.[43] A route to such motifs from **24n** via oxazoles **40** would surely be a welcome addition to the synthetic armamentary of the medicinal chemist.



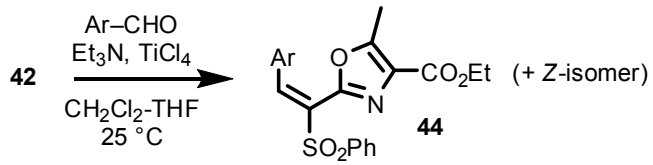
Scheme 10

With these objectives in mind, oxazole **24n** was desilylated and oxidized to the corresponding sulfone **42** (Scheme 11). Not unexpectedly, the anion of **42** failed to add to carbonyl compounds. However, smooth Knoevenagel condensation of **42** with aldehydes and even with ketones occurred in the presence of $TiCl_4$.[44] Aromatic aldehydes reacted best at room temperature in THF-CH_2Cl_2 in the presence of Et_3N. Products **44** formed mostly or exclusively as the *E*-isomers, consistent with the relative steric demand of an aryl, phenylsulfonyl, and 2-oxazolyl substituents.[45] Several examples appear in Table 5.



Scheme 11

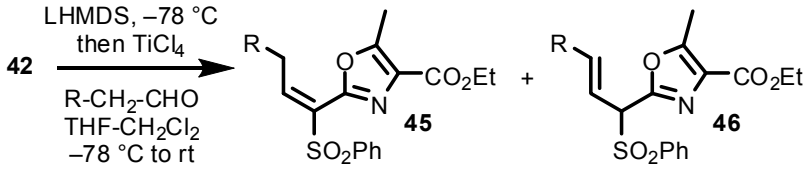
Table 5. Condensation of **42** with aromatic aldehydes



entry	Ar	E / Z ratio	% yield
a	Ph	*E* only	85
b	4-MeO-C_6H_4	7 : 1	93
c	4-HO-C_6H_4	*E* only	89
d	4-Cl-C_6H_4	*E* only	88
e	2-Me-C_6H_4	*E* only	88
f	2-Furyl	3 : 1	83
g	2-Thienyl	7 : 1	92
h	(*E*)-C_6H_5-CH=CH	1 : 1	76

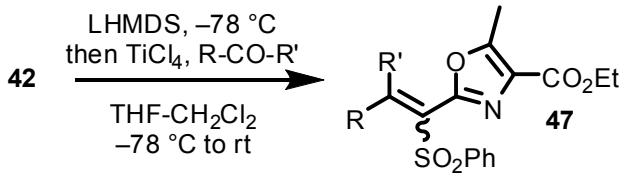
Reactions involving aliphatic aldehydes proceeded best when the carbonyl substrate and $TiCl_4$ were added to a cold (–78 °C) solution of lithiated **42**, prepared in advance by treatment with LHMDS,

Table 6. Condensation of **42** with aliphatic aldehydes



entry	R	45 : 46	% yield of 45	% yield of 46
a	C_6H_5-CH_2	2 : 1	60	30
b	Me	**45** only	87	--
c	*n*-C_5H_{11}	4 : 1	66	17

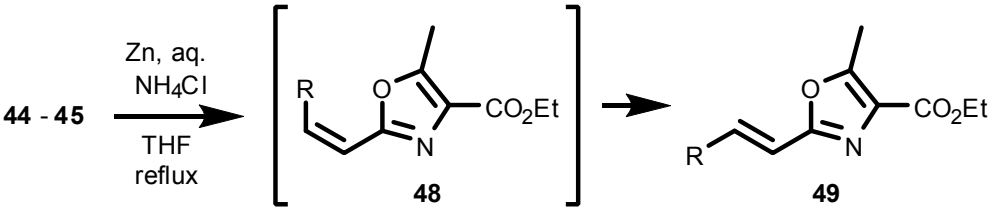
Table 7. Condensation of **42** with ketones



entry	RCOR'	*E* : *Z*	% yield
a	acetone	--	81
b	2-heptanone	5 : 1	78
c	cyclohexanone	--	85
d	acetophenone	4 : 1	44

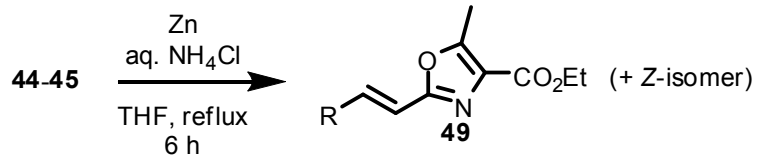
followed by gradual warming to room temperature. Enolizable aldehydes afforded mixtures of **45** (Table 6, major product, *E*-isomer only) and its deconjugated isomer **46** (*E*-isomer only), except propionaldehyde (entry **b**), which delivered only a product of the type **45**. Isomers **45** and **46** were readily separable by silica gel chromatography and were characterized independently. They were also prone to vinylsulfone-allylsulfone isomerization,[46] and care had to be taken to avoid this facile transposition. Identical operating conditions proved to be optimal for the reaction of ketones as well, except that no deconjugated products were observed with these substrates. Even unreactive acetophenone afforded the expected product in a respectable 44% yield. On the other hand, unsymmetrical ketones afforded mixtures of unassigned geometric isomers (Table 7; entries **b** and **d**).[47]

Whereas sulfones **44**-**47** may be valuable intermediates on their own right, a true olefination sequence required a simple, mild technique for their desulfonylation.[48] Happily, aldehyde-derived **44**-**45** underwent facile reductive desulfonylation by treatment with metallic Zn and aqueous NH_4Cl in refluxing THF (Scheme 12).[44] The use of Zn/NH_4Cl for the desulfonylation of compounds such as **44**-**45** was



Scheme 12

Table 8. Desulfonylation-isomerization of aldehyde-derived vinylsulfones **44**-**45**

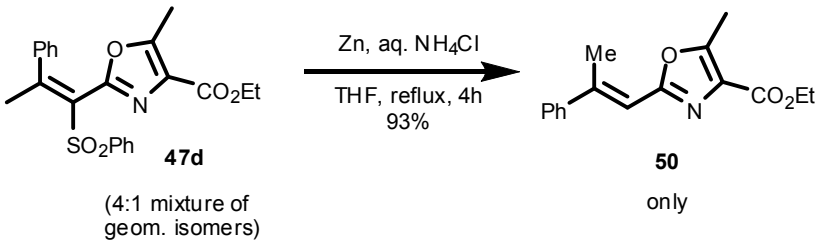


entry	R	*E* : *Z*	% yield
a	Ph	*E* only	100
b	4-MeO-C_6H_4	*E* only	94
c	4-HO-C_6H_4	*E* only	57
d	4-Cl-C_6H_4	*E* only	91
e	2-Me-C_6H_4	*E* only	93
f	2-Furyl	*E* only	89
g	2-Thienyl	*E* only	93
h	C_6H_5-$(CH_2)_2$	1 : 3.5	20 (*E*) + 70 (*Z*)
i	Et	1 : 3	23 (*E*) + 70 (*Z*)
j	*n*-C_6H_{13}	1 : 3	22 (*E*) + 66 (*Z*)

undocumented prior to our own work. No vinylsulfone-allylsulfone isomerization was detected during the reduction of **45** under such mild conditions.

The primary products of such reductive processes apparently formed with retention of olefin geometry; i.e. as the *Z*-isomers. Prolonged contact times (ca. 6 h) caused virtually complete isomerization of materials derived from aromatic aldehydes to the *E*-isomers. Substances emanating from aliphatic aldehydes isomerized more slowly, and were obtained as ca. 3:1 mixtures of *Z* (major) and *E* isomers. Table 8 summarizes the results of representive such desulfonylation-isomerization experiments. As for vinylsulfones **47**, the Zn/NH_4Cl system was effective only for the desulfonylation of products in which an aryl substituent was present on the olefin. For instance, **47d** afforded **50** in high yield and as the *E*-isomer

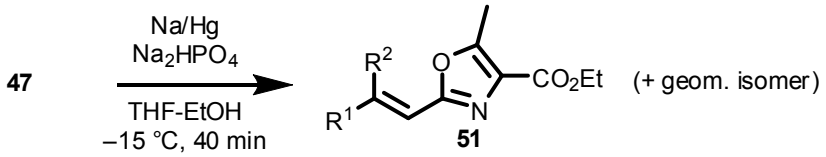
only (Scheme 13). By contrast, the desulfonylation of other ketone-derived products required the more vigorous reductant, Na/Hg amalgam, which is an established reagent for such transformations.[48]



Scheme 13

These reactions were best conducted at –15 °C for a short time (40 min.) to avoid overreduction. Yields were sensibly lower than in the previous case, as evident from Table 9. We presume that the difference in reactivity between **47d** and **47a-c** reflects relative LUMO energies: lower for **47d** thanks to phenyl conjugation; higher for **47a-c** due to the electron-releasing effect of alkyl substituents R^1 and R^2. Electron transfer into the less energetic LUMO is efficient with a weaker reductant such as metallic Zn; electron transfer into the more energetic LUMO requires a stronger reducing agent such as Na/Hg amalgam.

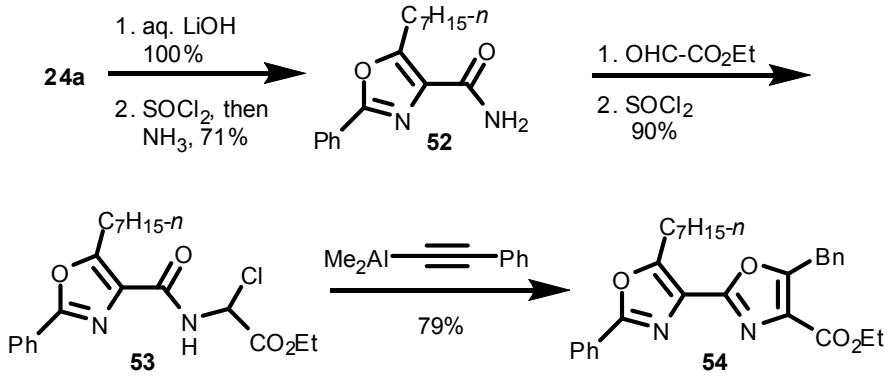
Table 9. Desulfonylation-isomerization of ketone-derived vinylsulfones **47a-c**



entry	R	R	isomer ratio	% yield
a	Me	Me	--	42
b	*n*-C_5H_{11}	Me	1 : 1	48
c	$(CH_2)_5$		--	49

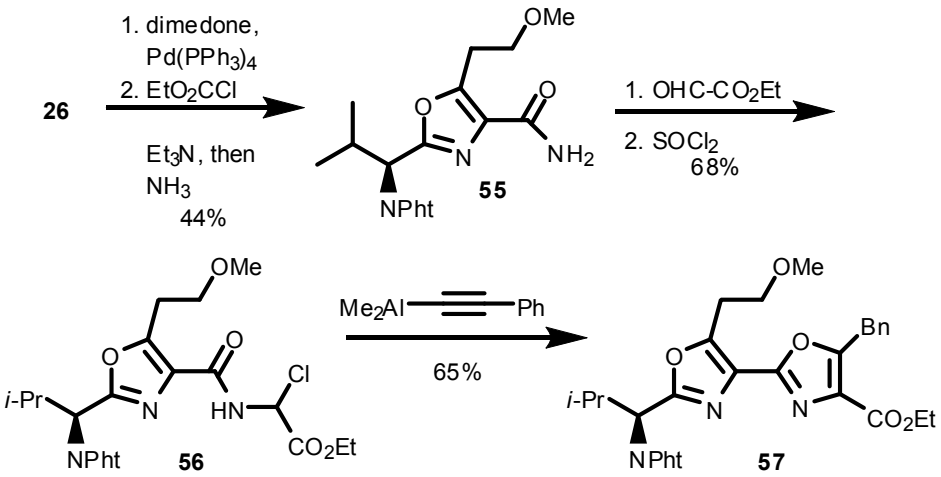
The iterative mode of oxazole assembly was demonstrated as shown in Schemes 14 and 15. Thus, **24a** and **26** were converted into the corresponding primary amides. These proved to be perfectly competent in a second round of the oxazole-forming reaction, leading to the production of bis-oxazoles **54** and **57** in 65-80% yield. Additional examples of bis-oxazole construction will be shown in the section dealing with

applications in natural product synthesis. We emphasize that in the course of experiments involving aminoacid-derived materials, great care was exercised to verify that no erosion of stereochemical integrity had taken place during the various transformations. Typically, this entailed the condensation (EDCI/



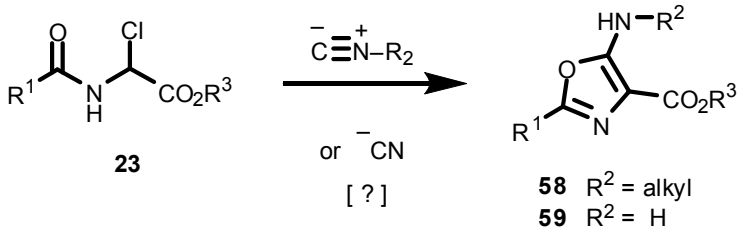
Scheme 14

HOBt) of oxazole carboxylic acids with (*R*)-methylbenzylamine, and careful scrutiny (^{1}H and ^{13}C NMR) of the resulting amide for diasteromeric homogeneity. No loss of optical purity was ever detected.



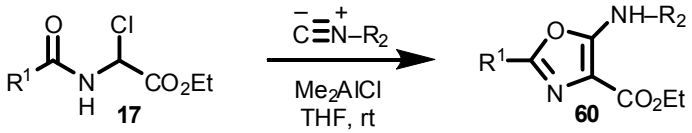
Scheme 15

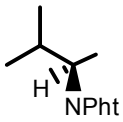
The favorable outcome of the foregoing investigations, as well as the work of Deyrup,[49] induced us to examine the reaction of chloroglycinates with isonitriles and cyanide ion, leading to the formation of 5-aminooxazoles (Scheme 16). Of course, the use of isonitriles as building blocks in oxazole synthesis is



Scheme 16

Table 10. Representative 5-alkylaminooxazoles obtained by the new method



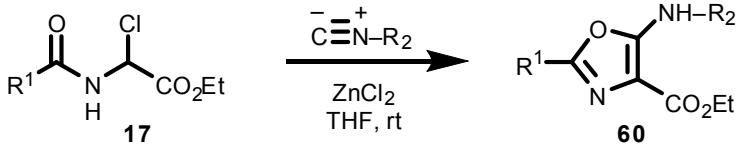
entry	R^1	R^2	% yield
a	Ph	*tert*-Bu	69
b	Ph	*n*-Bu	85
c	Ph	*c*-C_6H_{11}	75
d	Ph	Bn	78
e	Ph	$Ph(CH_2)_2$	61
f	Me	*n*-Bu	52
g	*c*-C_6H_{11}	*n*-Bu	77
h	Bn	*n*-Bu	56
i		*n*-Bu	74

well documented,[50] albeit not in the manner of Scheme 16. Accordingly, this chemistry would nicely complement existing alternatives.[51] Initial experiments determined that chloroglycinates do not combine

with isonitriles in the absence of Lewis acid promoters. Among the latter, $AlCl_3$ and ZnI_2 were ineffective, $ZnCl_2$ was moderately efficacious,[12] and Me_2AlCl proved to be outstanding, inducing the formation of the desired 5-alkylaminooxazoles in good to excellent yield (Table 10).[52]

The bioactivity of 5-aminooxazoles and their derivatives induced us to explore an automated synthesis using a robot such as the Chemspeed® system. For such a purpose, we elected to employ of the safer, if less efficacious, $ZnCl_2$ in lieu of the more effective, but pyrophoric, Me_2AlCl promoter. The Chemspeed® instrument, essentially a dispenser of liquids, would combine THF solutions of $ZnCl_2$, isonitriles, and chloroglycinates, then perform an extractive workup of the various reactions and purify the crude product by HPLC- MS.[53] We emphasize that neither the size of the library nor the yield of the final oxazole were of significant import at this juncture. Our objective was to demonstrate an automated route to oxazoles **60**

Table 11. Automated parallel synthesis of 5-alkylaminooxazoles by the new method

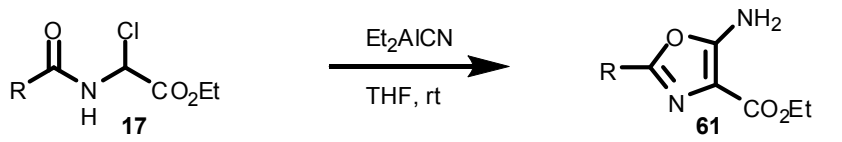


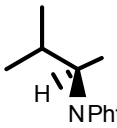
R^1 =	R^2 = *tert*-Bu	*n*-Bu	*cyclo*-C_6H_{11}	$PhCH_2$	2,6-Me_2-C_6H_3
Ph	–	Ã	–	Ã	Ã
Me	–	Ã	–	Ã	Ã
cyclo-C_6H_{11}	Ã	–	–	Ã	Ã
2-Me-C_6H_4	Ã	–	Ã	Ã	Ã
2,6-F_2-C_6H_3	–	Ã	–	Ã	Ã

of sufficient purity to permit screening. We thus chose to count as successful those reactions that afforded an oxazole of greater than 85% purity (HPLC-MS) in greater than 10% yield. The results of a parallel synthesis involving 5 chloroglycinates and 5 isonitriles are summarized in Table 11. A check mark indicates a successful reaction according to the foregoing criteria; a dash, that the reaction failed. It is apparent that two thirds of these automated syntheses were successful.[12]

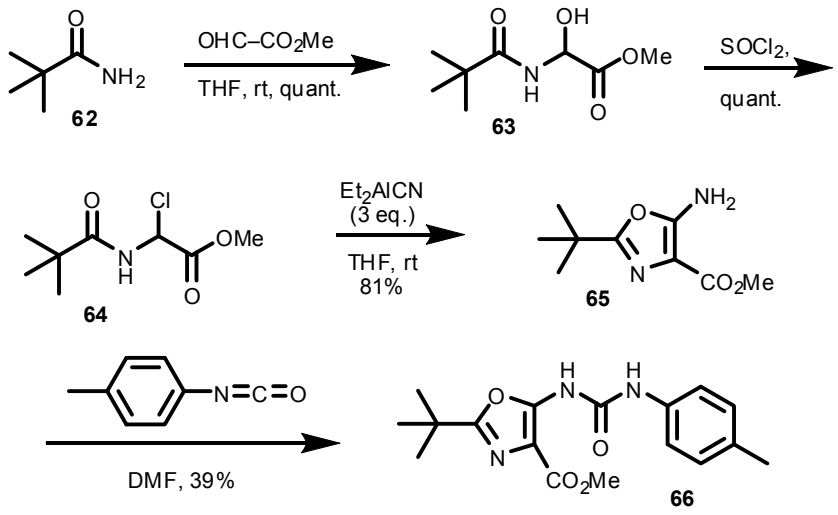
Turning now to the formation of 5-aminooxazoles, we found that exposure of chloroglycinates to the action of $Zn(CN)_2$, KCN, LiCN, $ZnCl_2$/KCN; $ZnCl_2$/TMSCN; Et_3N/KCN in THF, in a range of temperatures between 25 °C and reflux, failed to give any of the target heterocycles. However, efficient

Table 12. Representative 5-aminooxazoles obtained by the new method



entry	R	% yield
a	Ph	86
b	Me	36
c	*c*-C_6H_{11}	76
d	Bn	69
e		74

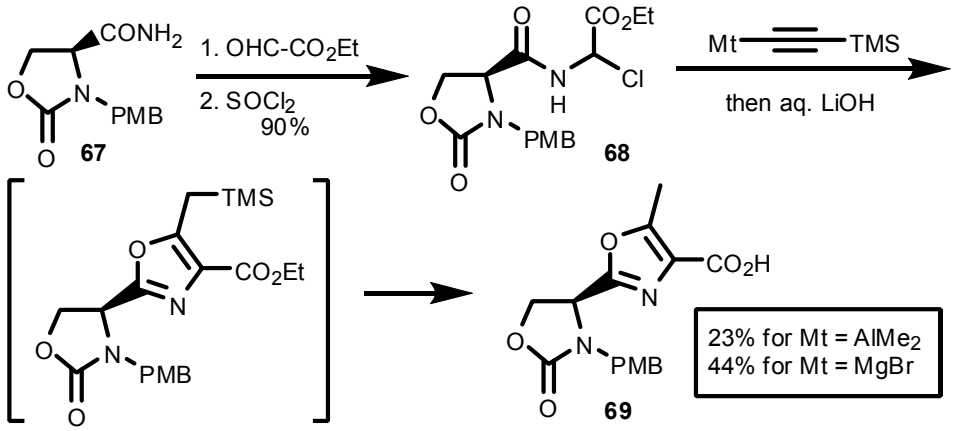
formation of the desired products ensued upon treatment with 3 equivalents of Et_2AlCN (Nagata reagent)[54] in THF, at rt. Table 12 provides representative examples of this transformation. An application of this chemistry was demonstrated through a synthesis of **66** (Scheme 17), a moderately potent inhibitor of Raf kinase,[55] and a possible point of departure for the development of new antitumor drugs.



Scheme 17

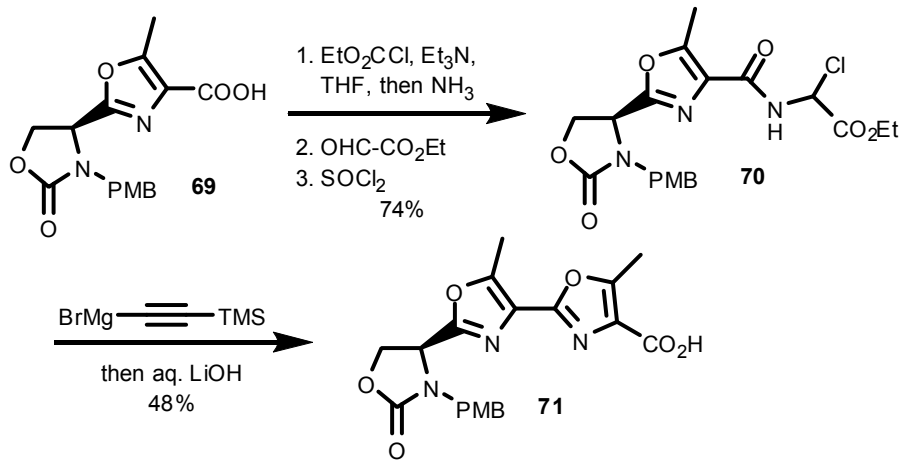
OXAZOLE FORMATION USING ALKYNYL GRIGNARDS: AN EXCEPTIONAL CASE

In one case uncovered thus far, an alkynyl Grignard reagent outperformed the corrsponding organoalane in the oxazole-forming reaction. Ongoing studies toward telomestatin require compound **71** (Scheme 19)



Scheme 18

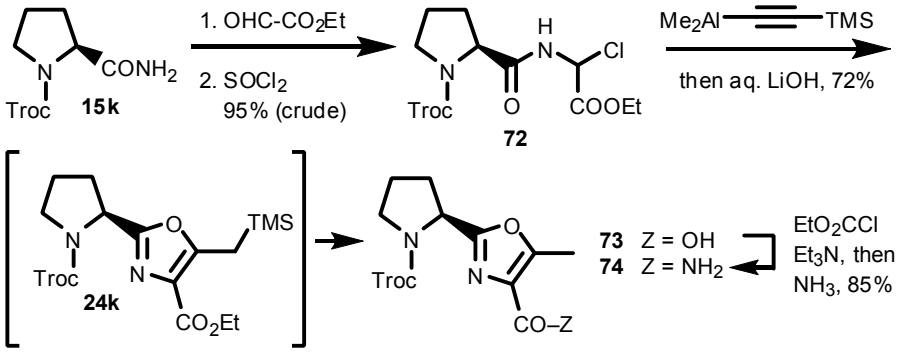
as the appropriate carrier of the bis-5-methyloxazole segment of the natural product. Experiments aiming to fashion the material in question from protected serine **67**[56] (Scheme 18) revealed that the reaction of chloroglycinate **68** with the dimethylaluminum derivative of TMS-acetylene was inefficient, affording the desired **69** in only 23% yield. The yield of this step doubled when the reaction was carried out with the corresponding acetylenic Grignard reagent. Notice how the LiOH workup of the oxazole-forming step serves to induce three distinct reactions: the complete cycloisomerization of the intermediate alkynylglycinate, the protiodesilylation of the primary product, and the saponification of the ester. Compound **69** was then elaborated to the requisite **71** as detailed in Scheme 19,[57] which demonstrates yet another iterative application of the oxazole-forming reaction.



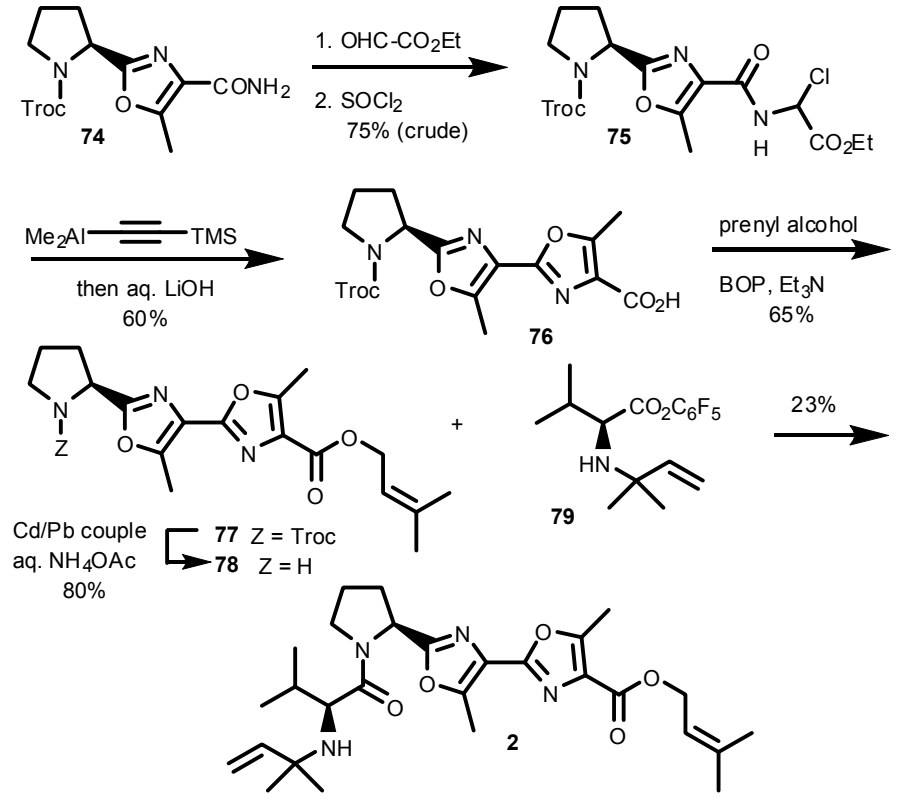
Scheme 19

APPLICATIONS IN NATURAL PRODUCT SYNTHESIS

An initial application of the new chemistry was demonstrated in the context of a total synthesis of the weak antibiotic, muscoride A, **2**.[18] This effort commenced (Scheme 20) with the elaboration of



Scheme 20

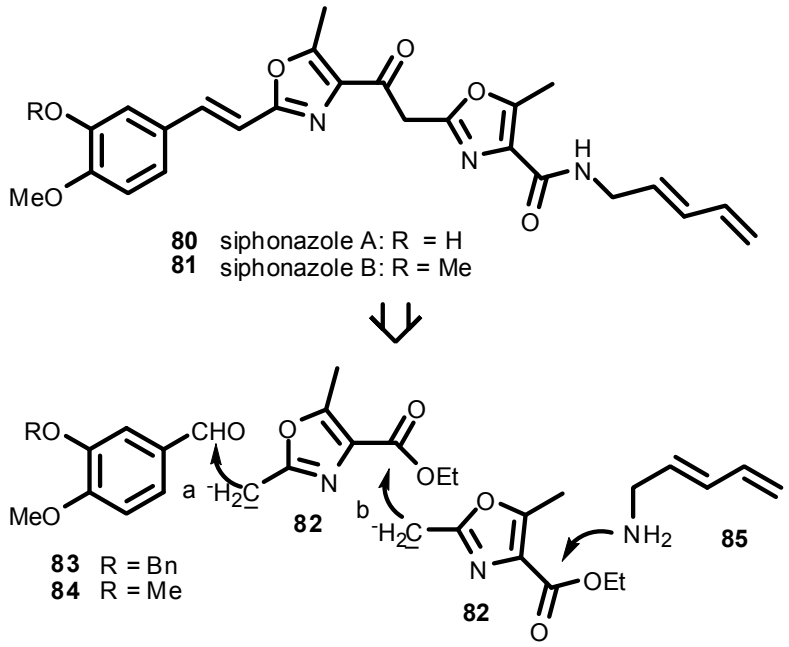


Scheme 21

(L)-proline to amide **15k** as a prelude to the execution of the first oxazole-forming sequence, which culminated with LiOH treatment of the nascent **24k**, providing acid **73** via simultaneous ester saponification/protiodesilylation. The acid was then converted into amide **74**, which was processed

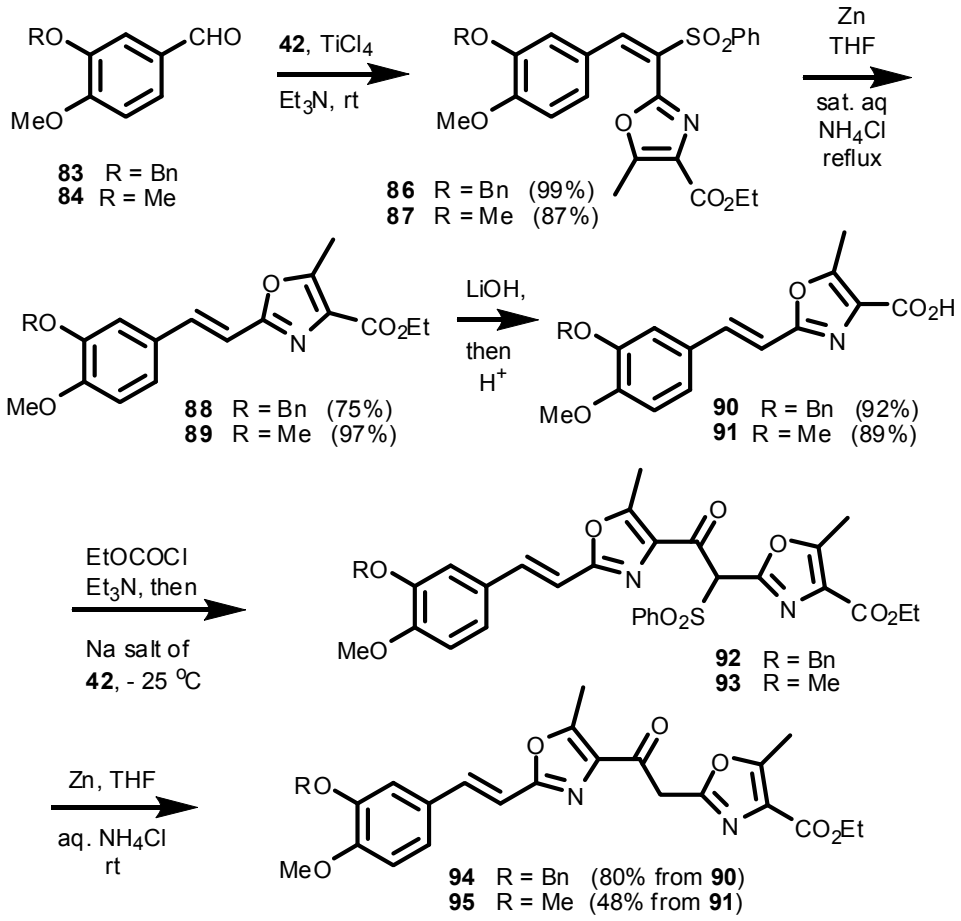
through a second oxazole iteration, as per Scheme 21. This surrendered acid **76**, which was esterified with prenyl alcohol, as required for the natural product. Finally, the Troc group was released under neutral conditions by the use of Cd/Pb couple,[58] and the synthesis was completed by acylation of **78** with activated ester **79** as described earlier by Wipf.[1]

A more recent effort has centered on the total synthesis of siphonazoles, **80**-**81**, which are structurally unusual bis-oxazole substances displaying a two-carbon bridge between the heterocyclic moieties.[59] Prior to their discovery, only compounds featuring directly linked oxazoles,[60] or oxazoles bridged by a single carbon atom,[61] were known among natural products. The structure of **80**-**81** evokes a possible iterative approach, wherein two copies of synthon **82** would merge with aldehyde **83 (**or its congener **84**) and amine **85** according to the format of Scheme 22. Clearly, sulfone **42** is an ideal carrier of synthon **82**. Consequently, bond **a** would be formed in a Julia-like mode as seen earlier, whereas bond **b** could be efficiently created by means of a Fujita acylation[62]/desulfonylation sequence.

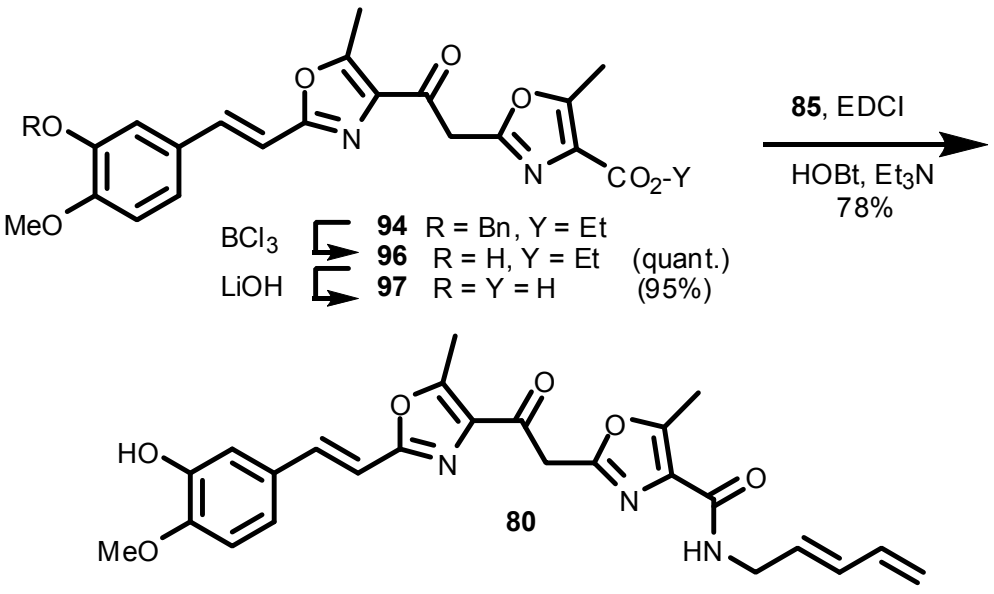


Scheme 22

The foregoing logic led to the identification of acids **90** and **91** (Scheme 23) as the first major subgoals of the synthesis. The construction of these segments unfolded uneventfully and in high overall yield. The practical nature of this sequence is apparent: no expensive reagents, strong bases or careful control of inert atmospheres are necessary. Acids **90** and **91** were then subjected to Fujita acylation/desulfonylation.

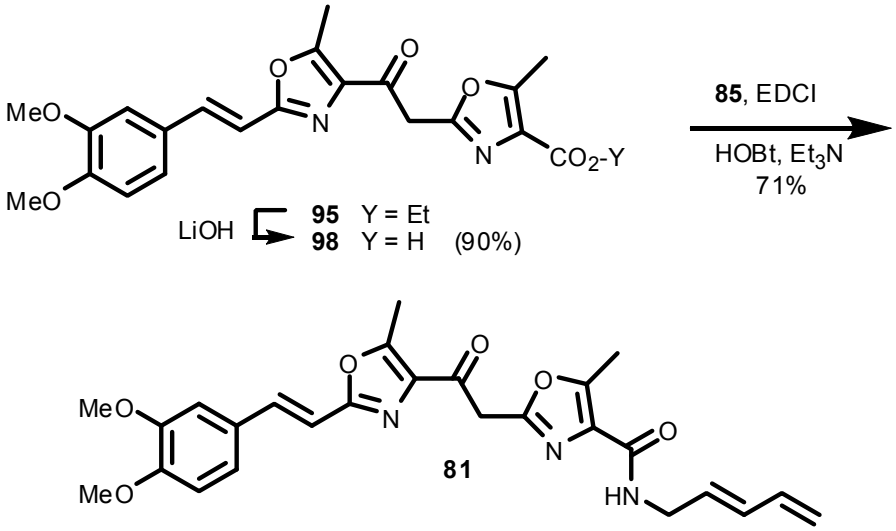


Scheme 23



Scheme 24

The crucial C–C bond forming step (cf. **90** → **92**) was found to afford superior results when a mixed anhydride was employed as the acylating agent in lieu of a more traditional acid chloride or acyl imidazole. The resultant ketosulfones **92** – **93** were best advanced to the following step in crude form, given their polar nature and C-acidity. Reductive desulfonylation to afford ketones **94** – **95** was achieved most efficiently with metallic Zn and aq. NH_4Cl as described by Holton.[63] The synthesis of siphonazole A was completed from **94** as illustrated in Scheme 24. Release of the benzyl ether and saponification of the ester afforded acid **96**, which upon coupling with amine **85**[64] delivered **80** in high overall yield. The synthesis of siphonazole B proceeded in a like fashion from **95** (Scheme 25).[65]



Scheme 25

We conclude this section by noting that synthetic siphonazoles obtained by the above routes were assayed for biological activity against various bacterial pathogens and tumor cell lines. What prompted these studies was the lack of information concering the biological properties of these natural products. At a test concentration of 10 μg/mL (NIH standard protocol; equivalent to $2.2 \bullet 10^{-5}$ M for **80** and $2.1 \bullet 10^{-5}$ M for **81**), both siphonazoles were moderately cytotoxic to human breast carcinoma (HTB-129), and, especially, human acute T-cell leukemia (TIB-152) cells, but they were inactive against hepatocellular carcinoma (hepG2), prostate cancer (PC3), colon adenocarcinoma (Caco-2) and Chinese hamster ovarian cancer (CHO) cell lines at the same concentrations. Siphonazole A is more active than its congener **81**. It induced cell death in human TIB-152 leukemia and mouse lymphoma cells with an IC_{50} value equal to 16 μg/mL ($3.5 \bullet 10^{-5}$ M), and in breast carcinoma NTB-129 with an IC_{50} of 20 μg/mL ($4.2 \bullet 10^{-5}$ M). Furthermore, it exhibited a good dose-response curve against human acute T cell leukemia TIB-152 and it was also cytotoxic against the mouse lymphoma cell line.[44]

CONCLUSION

The reactions described herein facilitate the construction of substituted oxazoles of interest in both natural products chemistry and drug research. We believe that in many cases the techniques described herein are superior to known alternatives for the synthesis of the target heterocycle. It is our hope that practitioners of synthetic heterocyclic chemistry in both industry and academia will make increasingly greater use of these methods.

ACKNOWLEDGMENT

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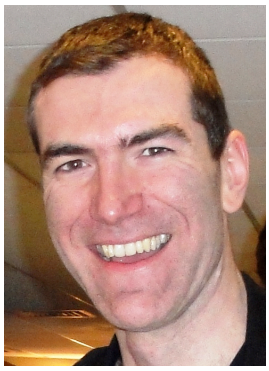

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